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KERATOCYSTIC ODONTOGENIC TUMOR-CYST OR TUMOR

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ABSTRACT

Background: Genetic and molecular research regarding odontogenic tumors, and KCOTs in particular, has led to an increasing amount of knowledge and understanding of their physio-pathological pathways.A review of the biological behaviour of this recognized aggressive pathological entity of the jaws and a contemporary outline of the molecular (growth factors, p53, PCNA and Ki-67, bcl-2) and genetic (PTCH,SHH) alterations associated with this odontogenic neoplasm provides a better understanding of the mechanisms involved in its development and strengthen the current concept that the KCOT should, indeed, be regarded as a neoplasm.

INTRODUCTION:

The head and neck region and the jaws in particular collectively comprise one of the common sites of occurrence of cysts. The frequency of cysts in the jaws is ascribed to the particular embryology of the facial skeleton and to the presence of teeth, which both pre and post-eruptively, may be associated with the epithelia and the epithelial residues potentially capable of being involved in the genesis of the cysts.(1)

Odontogenic cysts and tumors are lesions derived from odontogenic tissues. They comprise an unusually diverse group because odontogenesis is a complicated process in which cells in various stages of differentiation participate in a complex, predetermined manner. (2)

The Odontogenic Keratocyst (OKC) was first introduced as separate pathologic entity by “Philipsen” in 1956. These make up 11.2% of all the odontogenic cysts and have been considered to be developmental in origin. These are unique among odontogenic cysts because of their pathognomonic microscopic features, potentially aggressive clinical behaviour and high recurrence rate. (3)

In the earlier literature, the Keratocyst was described as a Cholesteatoma. In his detailed study on cysts, Forsell (1980) concluded that first account of this lesion was that of Mikulicz who in, 1876, described it as a Dermoid cyst. The term OKC was first introduced as separate pathologic entity by 'Philipsen' in 1956.The term 'Primordial cyst' was first mentioned in 1945 by Robinson. The designation keratocyst was used to describe any jaw cyst in which keratin was formed to a large extent. Some Dentigerous, Radicular and Residual cysts were therefore included in the category of OKC. Main DMG suggested a revision of 1971 WHO classification. As the histogenesis from the tooth primordium is not generally acceptable, the term odontogenic keratocyst is preferred to Primordial cyst and Dentigerous cyst is modified to follicular cyst. Shear M suggested a classification to the International Association of Oral Pathologists; in which the designation of odontogenic keratocyst was substituted for primordial cyst. (4)

In 1967, Toller suggested that the OKC may best be regarded as a benign neoplasm rather than a conventional cyst based on its clinical behaviour. In 1984, Ahlfors and others suggested that “if the OKC were recognized as a true, benign cystic epithelial neoplasia, the question of modified treatment schedules would be raised.” Significant differences on the molecular level between KCOT and other odontogenic cystic lesions suggested a different biological origin. (4)

In the years since, published reports have influenced WHO to reclassify the lesion as a tumour (Jonathan Madras 2008) and included it in the group of benign odontogenic tumours (OT) derived from odontogenic epithelium with mature, fibrous stroma without odontogenic ectomesenchyme (Barnes et al, 2005, LA GaitaCepeda 2010)

Several factors form the basis of this decision.

- **Behaviour:** As described earlier, the KCOT is locally destructive and highly recurrent.
- **Histopathology:** Studies such as that by Ahlfors and others show the basal layer of the KCOT budding mitotic figures are frequently found in the suprabasal layers.
- **Genetics:** PTCH (“patched”), a tumour suppressor gene involved in both NBCCS and sporadic KCOTs, occurs on chromosome 9q22.3-q31.36–40 PTCH binding to SMO inhibits growth-signal transduction. SHH binding to PTCH releases this inhibition. If normal functioning of PTCH is lost, the proliferation-stimulating effects of SMO are permitted to predominate

EPITHELIUM:

The histopathological features are distinctive and characteristic. The cysts are lined by a regular keratinized stratified squamous epithelium, which is thin and ranging from 5-8 cell layers.(4)

Basal layer is composed of a palisaded, polarized layer of cuboidal or columnar epithelial cells which are often hyperchromatic and often described as 'picket fence' or 'tombstone appearance'. Cuboidal basal cells occur relatively more frequently in relation to the orthokeratinized linings Flattened basal cells may also be found in some orthokeratinized linings (5,6,7)

Mitotic figures are found in the basal layer but more frequently in the suprabasal layers (Browne, 1971a), and mitotic activity is significantly greater in OKCs from patients with the NBCCS than from patients without (Woolgar et al., 1987a). Occasional linings show features of epithelial dysplasia (Rud and Pindborg, 1969) and some workers, while stressing that malignant transformation in jaw cysts was extremely rare, have made the point that keratinising cysts appear to have a greater tendency to such change than others. (8, 4)

Supra basal layers: The cells of suprabasal layer are polyhedral and often exhibit intracellular oedema; and intercellular bridges. The cells do not show a gradual flattening, and shows an abrupt transition between them and the keratin layer. Mitotic figures are found in the suprabasal layers more frequently than in the basal layers. (4)

Superficial layers: OKC lining is generally parakeratotic but sometimes it is orthokeratotic and both forms can be found in different parts of same cysts with considerable amounts of glycogen in the stratum granulosum. Shear M found that the stratum granulosum is more prominent in orthokeratinized variant of OKCs. (4,9)

Orthokeratinized OKC's represent 12%-13% of keratinizing odontogenic cysts and are more common in second to fifth decade of life with male predilection, occurring more frequently in mandible with a tendency for posterior part of jaw. The size can vary from less than 1 cm to as large as 7 cms. In the past, orthokeratinized odontogenic cysts were referred to as orthokeratinized variants of OKC's. However, since these lesions are clinically and microscopically different, so they are designated as Orthokeratinized Odontogenic Cysts. (6)

Epithelial Connective Tissue Interface:

The attachment between epithelium and the connective tissue capsule tends to be weak and in many areas separation occurs. The collapsed and folded thin walled cysts may give erroneous impression of multilocularity in histological sections. This zone of the cyst is potentially normal in its morphologic terms, but structurally different due to lack of collagen. This can be due to enzymatic degradation as suggested by Donoff et al that could interfere with the mechanical attachment of epithelium and connective tissue normally mediated by interrelationship of anchoring fibrils and collagen fibers. It could also be due to decreased rate of synthesis of collagen which interferes with attachment. (4, 10)

Ahlfors E et al reported that the infoldings of the keratocyst epithelium into capsule might be the result of the cyst epithelium being pushed into the capsule by active proliferation. The reorganization of the juxta epithelial collagen fibers may be favored by lysosomal enzyme activity. Thus these infolding results in the growth of the OKC.(11)

CONNECTIVE TISSUE CAPSULE:
The fibrous capsule is thin and often loose or myxoid with relatively few cells, which are separated by stroma, which is rich in mucopolysaccharides. Occasionally daughter cysts or epithelial islands are present in cyst wall, particularly when the patient has the jaw cysts, nevoid basal cell carcinoma syndrome. (12)

Vedtofte et al. showed the importance of the stroma in the growth of keratocysts on transplanted keratocyst epithelium in nude mice. The transplanted epithelium formed new cysts; however, the epithelium retained its typical histologic appearance only if supported by its own stroma. The authors suggested that the differentiation of the cystic epithelium is not independent of the stroma. Thus, it can be suggested that the biologic behaviour of keratocysts is dependent not only on the epithelium but also on the stroma (13)

Stenman G et al showed that the epithelium exhibits high activities of acid phosphatase and NADH diaphorase especially close to the proliferating fibroblast like cells, thus indicates a close relationship to the mesenchymal cells of the cystic capsule, which is essential for preservation of metabolic capacity.(14)

Smith G et al suggested that presence of immunoglobulins and immunoglobulins containing cells within the odontogenic cysts reflect that immunological reaction may have a role in its pathogenesis. IgG cells predominate over IgA cells. IgG plasma cells predominate in areas of diffuse chronic inflammation in tissues and increased IgA plasma cells is seen when the inflammation is more focal in nature. In infected cysts, bacterial products lead to specific and non-specific activation and proliferation of B cells and their subsequent differentiation into plasma cells, suggesting that odontogenic cyst fluids may be derived both as an inflammatory exudate and also from local synthesis in the cystic capsule.(15)

Smith G et al found that there are substantial numbers of mast cells in the connective tissue walls, and more prevalent just beneath the epithelium (sub epithelial zone) than in the deeper areas (intermediate and deeper areas) which play an important role in cyst enlargement. (16)

Role of inflammation:
Inflammation is a protective response intended to eliminate the initial cause of cell injury as well as the neurotic cells and tissues resulting from the original insult. (17). It involves a complex reaction to microbial, chemical, or physical agents in vascularized tissue resulting in the influx of circulating leukocytes, connective tissue cells, and extracellular constituents consisting of fibrous proteins (collagen, elastin) and glycoproteins (fibronectin, laminin, and proteoglycans). Chronic inflammation may develop from unresolved symptomatic acute inflammation or may evolve insidiously over a period of months without apparent acute onset of clinical manifestations (18)

Histopathologic features of chronic inflammation include the predominance of macrophages and lymphocytes, proliferation of nurturing structurally heterogeneous and hyperpermeable small blood vessels, fibrosis, and necrosis. Activated macrophages and lymphocytes are interactive in releasing inflammatory mediators or cytokines that amplify immune reactivity. Cytokines represent a family of biologic response modifiers including interleukins, chemokines, interferons, growth factors, and leukocyte colony stimulating factors. (18)

Inflammation has a puzzling effect on the epithelial lining of different origins. In several pathologic conditions, inflammation results in epithelial hyperplasia and metaplasia, such as radicular cysts, gastric epithelial-cell proliferation related to mucosal inflammation, prostatic hyperplasia, metaplasia in the nasal epithelium, and metaplastic polyp of the colon (19).

Although OKC is classified as a developmental lesion, inflammation is found in the connective tissue wall in the majority of cases (19). The presence of inflammation may be attributed to communications with the oral mucosa or by the periodontal ligament in cases where the cyst is close to adjacent teeth. However, the presence of inflammatory cells does not necessarily indicate the existence of secondary infection, it may be a tissue response induced by the epithelial lining. Fibroblasts have been shown to be active in recruiting inflammatory cells during the course of a normal response to tissue disruption by a neoplastic process (20,21)

Inflammation in the connective tissue stroma of the OKC is associated with the transition of the classic parakeratinized epithelium towards non-keratinizing squamous epithelium. The epithelium may proliferate to form rete ridges with the loss of the characteristic palisaded basal layer. When these changes involve most of the cyst lining, the diagnosis of odontogenic keratocyst cannot be confirmed unless other sections show the typical features described earlier (5). Inflammation has also been found to affect the proliferative potential of epithelial lining. It causes release of cytokines and growth factors that promote fibroblast proliferation and extracellular matrix production. (19)

Rodu et al in their study have shown that 76% of OKC's exhibit marked inflammation within the connective tissue cyst wall and that this is associated to a significant degree with transformation of the accompanying cyst lining to a non-keratinized form seen routinely in inflammatory odontogenic cysts. They hypothesized that this may influence a change in biologic behaviour to a less aggressive lesion, providing a rationale for further study of marsupialisation as a treatment option (22)

De Paula A M et al. in their study found a statistically significant increase of PCNA and Ki- 67 cells and of AgNOR numbers in the linings of inflamed odontogenic keratocysts compared to non-inflamed lesions. They concluded that inflammation induces an increase in the number of epithelial cells in cycle and that, the increased epithelial cell proliferation is associated with disruption of the typical structure of OKC linings. They suggested that growth factors and cytokines released by the inflammatory infiltrate present in the fibrous tissue capsule of OKCs may be responsible for greater proliferative activity in inflamed lesions compared to non-inflamed lesions. (23)

Hirshberg A et al conducted a study to investigate the influence of inflammation in the connective tissue wall of OKC on the polarization colors of the collagen fibers as viewed under polarizing microscope. They found that in the presence of dense inflammation, the percentage of thick fibers with green birefringence decreases, with an increase in thick fibers with red birefringence which appeared more packed. They concluded that inflammation has an impact on the packing of collagen fibers in the connective tissue wall of OKC as reflected by their birefringence colors under polarized light. (20)

GENETICS:
PTCH GENE: Morphogenesis and cyto-differentiation of the teeth are under genetic control of regulators such as Sonic Hedgehog (SHH), bone morphogenetic protein (BMP), Wnt, HGF, and FGF (24,25) and tumor-suppressor genes acting as regulators of cell growth (26). Inactivation of these genes by mutations and/or loss of heterozygosity (LOH) results in tumor development. Expression of Hedgehog signaling molecules - SHH, PTCH, smoothened (SMO), and GLI1 - has been detected in several odontogenic tumors, suggesting that SHH signaling pathway plays a role in epithelial-mesenchymal interactions and cell proliferation during the growth of odontogenic tumors as well as during tooth development (27,28)

PTCH ("patched"), a tumour suppressor gene involved in both NBCCS and sporadic KCOTs, occurs on chromosome 9q22.3-q31.36–40 Normally, PTCH forms a receptor complex with the oncogene SMO ("smoothened") for the SHH ("sonic hedgehog") ligand. PTCH binding to SMO inhibits growth-signal transduction. SHH binding to PTCH releases this inhibition. If normal functioning of PTCH is lost, the proliferation-stimulating effects of SMO are permitted to predominate. Aberrant activation of the SHH signalling pathway during adult life has been shown to be related to tumor formation. (29)

The SHH signaling pathway in the development of KCOT is not well known, although activation of this pathway may be related to the clinical behaviour and outcome of KCOT. The immunohistochemical analysis of the expression pattern of PTCH, SHH and SMO in sporadic KCOTs showed that the recurrence of KCOT is related to SMO expression. Yagyuu et al showed that the cases with strong SMO expression presented an higher Ki67 labeling than SMO-negative cases. (30)

GROWTH FACTORS: Li et al disclosed that the expression of epidermal growth factor receptor (EGFR) in odontogenic cyst was lower in epithelium adjacent to areas of inflammatory cell infiltration, with a most consistent staining of basal and suprabasal cells. The high levels of EGFR expression in KCOTs supported the view that they have an intrinsic growth potential not present in other odontogenic cysts. The lower EGFR expression reported both in the radicular cyst cells and the rests of Malassez from which they arise, contrasted with the maintenance of receptor expression in KCOTs which are derived from dental lamina remnants, which may reflect epithelial-mesenchymal interactions and growth factor/receptor modulation(31)

TGF-α has also been shown to be expressed mainly in the basal and suprabasal layers. of KCOTs compared with dentigerous and radicular cysts. Thus, expression levels of TGF-α, EGF and EGFR suggest involvement of the growth factors in their pathogenesis (32)

p53, PCNA and Ki-67: The proliferative activity of the lining epithelium of KCOTs has been the subject of various investigations aiming at the expression of p53, proliferating cell nuclear antigen (PCNA) and Ki67. Such studies concluded that p53, PCNA and Ki67 are more strongly expressed in KCOTs than in other types of odontogenic cysts. A number of immunohistochemical studies have examined KCOTs employing various markers of proliferation.

Slootweg et al suggested that the overexpression of p53 protein is related to the proliferative capacity of the KCOT rather than increased numbers of p53+ cells. (33)

Relatively low p53-positive ratio and a high TUNEL-positive ratio have been reported exclusively in the surface layer, which may substantiate that the decrease in p53- reactivity correlates with apoptosis in the surface layer. It has been postulated that p53 transmits apoptotic signals via a complicated mechanism, and DNA strand breaks are sensed by kinases leading to the

phosphorylation and activation of p5378, in which case p53 functions not only as an apoptosis-related protein but also as a marker of cellular proliferation KCOTs. (34)

Li et al results indicated the number of PCNA+ cells per unit length of basement membrane was found similar to that of parakeratinised oral epithelium, which let them to conjecture whether KCOT experienced a greater lateral rather than vertical migration of cells that might explain the consistently narrow and regular KCOT epithelium concomitant with active cyst growth. (35)

Ki-67 expression has been shown to be higher in the epithelium of KCOTs when compared to developmental and inflammatory cysts, with most of the Ki-67+ cells being detected in the suprabasal layers. These results demonstrate that cells constituting the intermediate or suprabasal layers possess the highest proliferative activity in the KCOTs. The correlation between Ki-67 and PCNA reflects cell proliferation.

Clonality Analysis: A distinguishing feature of a neoplasm is its origin from a single clone of genetically identical cells. Thus, defining clonality provides insight into the mechanisms of cellular proliferation and growth characteristics of "proliferative" lesions. Clonality can be inferred by referencing clonal markers such as the pattern of X chromosome inactivation in lesional tissue from female patients. The X-linked human androgen receptor (HUMARA) gene contains a polymorphic DNA marker that reliably illustrates the pattern of X chromosome inactivation in a tissue. Gomes et al. (2009b) investigated the clonal origin of 19 cases of odontogenic tumors, including 6 cases of OKC. Among the 16 informative cases, 12 showed a monoclonal pattern. Four of the six OKCs were monoclonal, and the remaining two were polyclonal. While emphasizing that most odontogenic tumors are clonal, including OKCs, the authors did attribute the four polyclonal cases to the contamination of samples by stromal or inflammatory cells. The two polyclonal OKCs contained a significant dispersed inflammatory cell component. These findings do indicate that considerable numbers of OKCs are composed of a monoclonal population of cells, lending support for their neoplastic nature. (36)

Apoptotic mechanisms: Previous reports comparing apoptosis related factors in sporadic KCOTs and KCOTs associated with nevoid basal cell carcinoma have been published (37) and apoptotic cells have been found in the superficial cells of the lining epithelia of KCOTs through the TdT-mediated dUTP-biotin nick end labelling (TUNEL) method.

Among all proto-oncogenes, bcl-2, located at chromosome 18q21, is characteristically able to stop programmed cell death (apoptosis) without promoting cell proliferation. Its gene product, the bcl-2 protein, acts as a cell death suppressor that facilitates cell survival by regulating apoptosis. (28)

Investigations on the immunoreactivities of bcl-2 protein have been demonstrated in tooth germs, ameloblastomas, KCOTs and dentigerous cysts. Recent studies report that bcl-2 positive cells are predominantly located basally, thus supporting the concept that apoptosis does not occur in the basal cells of the lining epithelium. (37,38)

TUNEL-positive cells have been detected exclusively in the surface layer of KCOTs, indicating marked levels of apoptosis. Thus, bcl-2 inhibits apoptosis to facilitate cellular proliferation in the basal and suprabasal layers, whereas apoptosis maintains the homeostasis of the thickness of the lining epithelium and allows the synthesis of large amounts of keratin in the surface layer of KCOTs.

Considering that there is a regulated balance between cell proliferation, cell differentiation and cell death in this type of lesion, this may explain why KCOTs, though portraying a neoplastic behaviour, with an increase potential to proliferate, do not tend to form tumor masses.

CONCLUSION:

A review of the histopathological features and biological behaviour of this recognized aggressive pathological entity of the jaws and a contemporary outline of the molecular (growth factors, p53, PCNA and Ki-67, bcl-2) and genetic (PTCH, SHH) alterations associated with this odontogenic neoplasm provides a thorough understanding of the physiopathological mechanisms involved in the development of this neoplasm of the jaws. There are, indeed, significant differences on the molecular level between KCOT and other odontogenic cystic lesions, suggestive of a different biological behaviour.

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